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(54) **LIQUID PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF A POSTERIOR EYE DISEASE**

FLÜSSIGE PHARMAZEUTISCHE ZUSAMMENSETZUNG ZUR BEHANDLUNG VON ERKRANKUNGEN DES HINTEREN AUGES

COMPOSITION PHARMACEUTIQUE LIQUIDE DESTINÉE AU TRAITEMENT D'UNE MALADIE DE L'OEIL POSTÉRIEUR

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(56) References cited:
US-A- 5 336 175 US-A- 5 518 731
US-B1- 6 262 126

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- MEINERT H ET AL: "Semifluorinated alkanes--a new class of compounds with outstanding properties for use in ophthalmology", EUROPEAN JOURNAL OF OPHTHALMOLOGY, MILAN, IT, vol. 10, no. 3, 1 July 2000 (2000-07-01), pages 189-197, XP009134460, ISSN: 1120-6721 cited in the application
- HOERAUF H ET AL: "Combined use of partially fluorinated alkanes, perfluorocarbon liquids and silicone oil: An experimental study", GRAEFE'S ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, SPRINGER VERLAG, XX, vol. 239, no. 5, 1 June 2001 (2001-06-01), pages 373-381, XP008112947, ISSN: 0721-832X, DOI: DOI:10.1007/S004170100264 [retrieved on 2001-05-05]
- DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; June 2009 (2009-06), PINARCI E Y ET AL: "Intraocular gas application in the diagnosis and treatment of valsalva retiopathy in a case with premacular hemorrhage", XP002625604, Database accession no. EMB-2010460971 & RETINA-VITREUS 2009 GAZI EYE FOUNDATION TUR, vol. 17, no. 2, June 2009 (2009-06), pages 153-155, ISSN: 1300-1256

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Description

BACKGROUND

- 5 **[0001]** The present invention relates to pharmaceutical compositions in liquid form which are suitable for the delivery of active ingredients to the posterior segment of an eye.
- [0002]** Today, ophthalmic diseases affecting tissues of the posterior segment of the eye are responsible for most cases of irreversible blindness worldwide. These include conditions such as glaucoma, age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa.
- 10 **[0003]** Glaucoma is a disease characterised by severe damage to the optic nerve leading to progressive, potentially irreversible loss of vision. The damage involves loss of retinal ganglion cells in a characteristic pattern. Glaucoma is often, but not always, associated with increased ocular pressure. According to WHO estimates, the disease contributed to more than 12 % of all causes for blindness globally in 2002.
- [0004]** Age-related macular degeneration accounted for 8.7 % of blindness worldwide in 2002. It is a condition involving damage to the retina in a pattern that leads to a loss of vision in the centre of the visual field, also known as the macula.
- 15 **[0005]** Diabetic retinopathy is an ocular condition which affects up to 80 % of all patients who have had diabetes for 10 years or more, and accounts for about 5 % of the incidence of blindness worldwide. The retinopathy is the result of microvascular retinal changes. A hyperglycaemia-induced death of ocular pericytes leads to capillary wall damage and potentially oedema, such as macular oedema. In the absence of treatment, blurred vision and eventually blindness may develop as a result.
- 20 **[0006]** Retinitis pigmentosa describes a group of ophthalmic diseases which have a genetic origin, and which are characterised by progressive retinal dystrophy, i. e. a degeneration of the photoreceptors or the retinal pigment epithelium resulting in a loss of vision. The condition often becomes manifest in the form of impaired dark adaptation or nyctalopia, often followed by reduction of the peripheral visual field. At a progressed stage of the disease, it may involve the loss of central vision.
- 25 **[0007]** For at least some of the diseases affecting the tissues of the posterior segment of the eye, it may be possible to slow their progression, reduce the severity of symptoms, or even substantially control the condition by pharmacotherapy. For example, in the case of glaucoma, several classes of active agents have been used with significant success, including prostaglandin analogs (such as latanoprost, bimatoprost, and travoprost), beta-adrenergic receptor antagonists (such as timolol, levobunolol, and betaxolol), alpha-2-adrenergic agonists (such as brimonidine), and carbonic anhydrase inhibitors (such as dorzolamide, brinzolamide, and acetazolamide).
- 30 **[0008]** The effective delivery of active agent to the posterior eye, however, remains to be a major problem in ophthalmology. Most commonly, ophthalmic pharmacotherapy relies on the topical administration of - typically liquid - formulations to the front of the eye. Most patients are well familiar with eye droppers, their use is perceived as relatively simple and convenient, and the non-invasive nature of the topical route makes it predestined for self-administration.
- 35 **[0009]** On the other hand, only a small fraction of a topically administered drug substance - typically less than about 5 % - reaches the location where its pharmacological activity is required. Only a fraction of the volume of a formulation which is administered (which is usually about 30 to 50 μ l) due to the limited volume capacity of the lacrimal sac: a significant fraction of the administered fluid volume is expelled by the blinking of the eyelids, and another fraction is taken up systemically via the nasolacrimal duct, which potentially leads to adverse drug effects. The fraction of the drug substance which does reach the posterior segment of the eye after topical administration into the fornix of the conjunctiva must first diffuse through the lacrimal film, the cornea (which represents a major barrier for most drugs), the anterior aqueous chamber, and the vitreous chamber, which diffusion path is characterised by a relatively small area, a relatively long diffusion distance, and several competing pathways which lead to drug loss. Depending on the nature of a drug substance, it may therefore be rather challenging to obtain therapeutic concentrations in the posterior segment of the eye.
- 40 **[0010]** In recent years, a number of alternatives to the topical route of ophthalmic delivery have been investigated. In particular, new methods, devices and compositions for intraocular and periocular administration have been proposed.
- [0011]** Intravitreal injections are the most direct approach to drug delivery to the posterior segment, and it is much more likely to obtain and maintain therapeutic drug levels following such type of injection than after topical delivery. A drawback of this route is that the vitreous liquid undergoes some relatively rapid turnover, so that drugs introduced into it are quickly eliminated. At the same time, intravitreal injections require the service of a specialised physician; they are clearly unfeasible for self-administration or for administration by a nurse. For patients, the mode of injection is highly uncomfortable and may be substantially painful in spite of local anaesthesia. Since many of the conditions affecting the posterior eye are of chronic or sub-chronic nature, intravitreal injection would have to be performed on a regular basis, which is even less acceptable to patients and brings about some considerable risk of iatrogenic eye infections and damage to the eye.
- 45 **[0012]** In order to somewhat improve patient convenience, depot formulations for intravitreal administration have been developed. These are still injected into the eye ball, or perhaps even require more extensive ophthalmic surgery to insert
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(and to remove, depending on the particular delivery system), but the frequency of administration can be substantially reduced. Among the proposed formulation designs are colloidal drug carriers such as liposomes, dendrimers, polymeric microparticles, and gels, but also solid implants, such as disclosed in WO 2010/062394 and WO 2008/060359. These delivery systems may provide for drug release over periods of several days, weeks, or months, depending on the nature of the drug carrier.

[0013] To avoid the inconvenience and risks associated with intravitreal injections, various forms of periocular administration have been developed as alternatives. These include in particular sub-Tenon's, subconjunctival or retrobulbar injections. This approach to drug delivery is considered safer and somewhat less invasive than intravitreal injection and also offers some potential for localised drug depots. The sub-Tenon's injection technique typically uses a short needle introduced through the superotemporal bulbar conjunctiva into the sub-Tenon's space while the patient is instructed to look inferonasally. The cannula is then advanced posteriorly along the globe in a gently sweeping motion to prevent accidental eyeball penetration until the hub reaches the conjunctival entry site, when the formulation is discharged. In a typical subconjunctival injection procedure, a needle is inserted and the medication delivered into the space between the conjunctiva and the sclera. Retrobulbar injections are frequently administered for providing local anaesthesia. A medium-short needle is inserted at the inferolateral border of the bony orbit and advanced straight back for about 1.5 cm until it has passed the equator of the globe. Then it is directed medially and upwards toward the apex of the orbit, penetrating the muscle cone delineating the retrobulbar space. Several millilitres of injection volume can be delivered to this site.

[0014] However, it is obvious that also these injection techniques, even though perhaps somewhat less distressing than intravitreal injections, are not at all convenient to patients or free of risk with respect to inadvertent bulb penetration or infection.

[0015] Thus there remains a clear need for improved delivery methods for drugs which act in the posterior segment of the eye. More specifically, there is a need for methods having a potential to achieve more target-specific, effective delivery of therapeutic compounds to the tissues of the posterior eye. In particular, there is a need for methods which overcome one or more of the disadvantages of the currently known ophthalmic drug delivery methods. Moreover, methods are needed which are safer and more convenient than the currently practised methods. In a further aspect, there is a need for pharmaceutical compositions and kits which are useful for practising such improved methods.

[0016] It is therefore an object of the present invention to provide such improved delivery methods for active ingredients acting in the posterior eye. A further object is to provide methods which overcome one or more disadvantages that are associated with the commonly known and practised delivery methods. In a further aspect, it is an objective of the invention to provide pharmaceutical compositions which are suitable for carrying out such methods. These and further objects will become clear on the basis of the description of the invention and the patent claims. Any references in the description to treatments or to methods of treatment refer to the compositions of the present invention for use in a method of treatment.

SUMMARY OF THE INVENTION

[0017] The present invention provides a pharmaceutical composition as defined in the claims for use in the treatment of a disease or condition of a tissue associated with the posterior segment of an eye of a patient. The composition is administered by periocular injection, followed by a second step of bringing the patient into a supine position facing upwards for a sufficiently long time period to allow the composition to migrate from the site of administration to a site in the posterior segment of the eye.

[0018] The method and composition of the invention may be used to provide for sustained release of an incorporated active ingredient to the posterior segment of an eye, and are beneficial in the management of various eye diseases such as age-related macular degeneration, diabetic retinopathy, glaucoma, retinitis pigmentosa, and cytomegalovirus retinitis.

DETAILED DESCRIPTION OF THE INVENTION

[0019] As used herein, the posterior segment of the eye comprises any ophthalmic tissue or structure posterior to (and including) the anterior hyaloid membrane, such as the vitreous humor, the retina, the choroid, the sclera, the retinal blood vessels, the optic disk, the hyaloid canal, and the optic nerve.

[0020] A pharmaceutical composition is a composition of typically at least one active pharmaceutical compound and one or more excipients which is useful in the prevention, diagnosis, stabilisation, treatment, or - generally speaking - management of a condition or disease. As used herein, treatment refers to any type of pharmaceutical use of such composition, including any prophylactic or preventive use, and in particular any use for stabilising, managing, or curing a disease or pathological condition, or the improvement of symptoms associated therewith.

[0021] A liquid vehicle is understood as a liquid excipient or mixture of excipients serving as a carrier for an active ingredient and enabling its proper administration. A liquid vehicle is liquid at normal temperature, but of course may be solid at lower temperatures. Non-aqueous refers to the property of being substantially free of water. However, this does

not exclude the presence of residual amounts of water as commonly contained in non-aqueous organic liquids. Physiologically tolerable means that a vehicle or excipient is acceptable for pharmaceutical use in consideration of the intended route of administration, frequency of use, severity of the condition that is treated, and amount of vehicle administered per dosing.

[0022] An important feature of the invention is the high density of the non-aqueous vehicle comprised in the pharmaceutical composition. In essence, the density of the vehicle is selected to be substantially higher than that of physiological fluids, including the lacrimal fluid as well as the interstitial fluid, which are both rather similar to water or slightly denser than water. In contrast, the density of the non-aqueous vehicle according to the invention is much higher, at least 1.2 g/cm³. In a further embodiment, the density of the vehicle is at least about 1.25 g/cm³, 1.3 g/cm³, or 1.35 g/cm³, respectively. Moreover, it is preferred that the density of the pharmaceutical composition as a whole is, by virtue of its content of the dense non-aqueous vehicle, also substantially higher than that of water, such as at least about 1.2 g/cm³, 1.25 g/cm³, in particular at least about 1.3 g/cm³.

[0023] The composition is administered by periocular injection. Such periocular injection may be carried out as sub-Tenon's or subconjunctival injections, as described hereinabove.

[0024] After receiving the composition, the patient is placed in a supine position, or instructed to bring himself into a supine position, holding the face upwards. It may not be necessary that the whole body of the patient is supine as long as the head is in the required position. Unexpectedly, the inventors have found that - probably by virtue of the high density of the non-aqueous vehicle, even though they do not wish to be bound by this theory - the supine position of the head effects a migration of the periocularly administered composition towards the retrobulbar region where it forms a depot from which an active ingredient incorporated within the composition is released gradually over time. The effect is most pronounced if the vehicle is selected to be substantially water-immiscible. The supine position must be maintained for a sufficiently long period of time to allow the composition, or at least a pharmacologically relevant fraction thereof, to migrate from the site of administration to the site in the posterior segment of the eye. The exact duration required for this to happen depends, *inter alia*, on the precise mode of administration, the actual density of the composition, and its volume. In one of the preferred embodiments, the supine position is maintained over at least about 15 minutes. In another embodiment, it is maintained over at least about 30 minutes, or at least about 1 hour, or at least about 2 hours, 3 hours, 4 hours, or 6 hours, respectively.

[0025] As mentioned, a key feature of the invention is that the non-aqueous vehicle used in the composition has a particularly high density, and in a preferred embodiment, the density of the whole composition is also particularly high, i.e. substantially higher than that of the aqueous fluids of the body. It is also preferred that the dense non-aqueous vehicle makes up most of the liquid phase of the composition, such as at least about 60 wt.-%, and more preferably at least about 80 wt.-%, or at least about 90 wt.-%, or at least about 95 wt.-%. In a particularly useful embodiment, the liquid phase of the composition consists of the non-aqueous vehicle having a density as described above, which however would not exclude the presence of some residual amounts of other liquids having little or no technical impact.

[0026] The liquid vehicle is a semifluorinated alkane as defined in the claims. Semifluorinated alkanes are linear or branched alkanes some of whose hydrogen atoms have been replaced by fluorine. In a preferred embodiment, the semifluorinated alkanes (SFA's) used in the present invention are composed of at least one non-fluorinated hydrocarbon segment and at least one perfluorinated hydrocarbon segment. Particularly useful are SFA's which have one non-fluorinated hydrocarbon segment attached to one perfluorinated hydrocarbon segment, according to the general formula $F(CF_2)_n(CH_2)_mH$, or two perfluorinated hydrocarbon segments separated by one non-fluorinated hydrocarbon segment, according to the general formula $F(CF_2)_n(CH_2)_m(CF_2)_oF$.

[0027] Another nomenclature which is used herein refers to the above-mentioned SFA's having two or three segments as RFRH and RFRHRF, respectively, wherein R_F designates a perfluorinated hydrocarbon segment, R_H designates a non-fluorinated segment. Alternatively, the compounds may be referred to as F_nH_m and F_nH_mF_o, respectively, wherein F means a perfluorinated hydrocarbon segment, H means a non-fluorinated segment, and n, m and o is the number of carbon atoms of the respective segment. For example, F3H3 is used for perfluoropropylpropane. Moreover, this type of nomenclature is usually used for compounds having linear segments. Therefore, unless otherwise indicated, it should be assumed that F3H3 means 1-perfluoropropylpropane, rather than 2-perfluoropropylpropane, 1-perfluoroisopropylpropane or 2-perfluoroisopropylpropane.

[0028] The semifluorinated alkanes according to the general formulas $F(CF_2)_n[CH_2]_mH$ and $F(CF_2)_n[CH_2]_m(CF_2)_oF$ have segment sizes ranging from 3 to 20 carbon atoms, i.e. n, m and o are independently selected in the range from 3 to 20. SFA's which are useful in the context of the present invention are also described in EP-A 965 334, EP-A 965329 and EP-A 2110126.

[0029] In a further embodiment, the semifluorinated alkane is a compound according to the formula RFRH, whose segments R_F and R_H are linear and each - but independently from one another - have from 3 to 20 carbon atoms. In another particular embodiment, the perfluorinated segment is linear and comprises from 4 to 12 carbon atoms, and/or the non-fluorinated segment is linear and comprises from 4 to 8 carbon atoms. Preferred SFA's include in particular the compounds F4H5, F4H6, F6H4, F6H6, F6H8, and F6H10. Presently most preferred for carrying out the invention are

F4H5, F6H6 and F6H8.

[0030] Optionally, the composition may comprise more than one SFA. It may be useful to combine SFA's, for example, in order to achieve a particular target property such as a certain density or viscosity. If a mixture of SFA's is used, it is furthermore preferred that the mixture comprises at least one of F4H5, F4H6, F6H4, F6H6, F6H8, and F6H10, and in particular one of F4H5, F6H6 and F6H8. In another embodiment, the mixture comprises at least two members selected from F4H5, F4H6, F6H4, F6H6, F6H8, and F6H10, and in particular at least two members selected from F4H5, F6H6 and F6H8.

[0031] Liquid SFA's are chemically and physiologically inert, colourless and stable. Their typical densities range from 1.1 to 1.7 g/cm³, and their surface tension may be as low as 19 mN/m. SFA's of the RFRH type are insoluble in water but also somewhat amphiphilic, with increasing lipophilicity correlating with an increasing size of the non-fluorinated segment. Again, for practising the current invention, an SFA having a density of at least 1.2 g/cm³ should be selected.

[0032] Liquid SFA's of the RFRH type are being used commercially for unfolding and reapplying a retina, for long-term tamponade as vitreous humor substitute (H. Meinert et al., European Journal of Ophthalmology, Vol. 10(3), pp. 189-197, 2000), and as wash-out solutions for residual silicon oil after vitreo-retinal surgery. Experimentally, they have also been used as blood substitutes (H. Meinert et al., Biomaterials, Artificial Cells, and Immobilization Biotechnology, Vol. 21(5), pp. 583-95, 1993). These applications have established SFA's as physiologically well tolerated compounds. On the other hand, SFA's have not been used as excipients in approved drug products as of today.

[0033] It has now surprisingly been found by the inventors that SFA's having the specified density are particularly suitable as carriers, vehicles or excipients in ophthalmic compositions for topical or minimally invasive administration. This is not only based on the observation that the respective compositions are capable of migrating towards the posterior segment of the eye after administration, but also on the fact that SFA's are capable of dissolving many poorly water-soluble compounds which are of interest in ophthalmology. Moreover, they are unexpectedly well-tolerated by the eye, as shown in preclinical testing. This is very surprising as many organic or non-aqueous solvents, perhaps with the exception of oily compounds and the vehicles specified in the context of the invention, are typically very irritating or even highly damaging when administered topically to an eye.

[0034] Compared to oily carriers or vehicles in ophthalmic compositions for topical use, SFA's exhibit a refractive index which is much better compatible with the aim of a minimally affected vision: While oily preparation lead to a blurry vision and can therefore not be administered in any situation in which the patient needs a clear vision, SFA's cause little or no blurring.

[0035] By illustration, the refractive index of tear fluid is close to that of water, i.e. 1.333 at room temperature (RT). Oils typically have a substantially higher refractive index such as about 1.46 (peanut oil), 1.47 (sesame oil), or 1.48 (castor oil). In contrast, the inventors have determined the refractive indices of various SFA's of interest to be in the region of 1.29 to 1.35, i.e. much closer to that of water. In one of the specific embodiments, the invention is therefore practised with an SFA whose refractive index is from 1.29 to 1.35, and in particular from about 1.30 to about 1.35 at 20°C. The refractive index for selected SFA's is shown in table 1.

[0036] Moreover, SFA's exhibit a remarkable wetting and spreading behaviour by which they deliver an incorporated active ingredient rapidly and effectively to the corneal surface and conjunctiva. Wetting means the ability of a liquid to establish and maintain contact with a solid surface, resulting from intermolecular interactions when the two are brought together. The balance between adhesive and cohesive forces determines the degree of wetting. The higher the adhesive forces compared to the cohesive forces, the more a drop of liquid will spread across the surface of the solid material. Conversely, very high cohesive forces within the liquid will cause the drop to form a sphere, thus avoiding contact with the surface. Similarly, spreading may also occur at the interface of two liquids which are brought into contact with each other.

[0037] A measure for wetting and spreading is the contact angle θ . The contact angle is the angle at which the liquid-vapour interface meets the solid-liquid or liquid-liquid interface. The tendency of a drop to spread out increases as the contact angle decreases. Thus, the contact angle provides an inverse measure of wettability.

Table 1

SFA	Refractive index
F4H4	1,308
F4H5	1,3204
F4H6	1,334
F4H7	1,3357
F4H8	1,348
F6H2	1,295
F6H4	1,306
F6H6	1,3224

(continued)

SFA	Refractive index
F6H7	1,3366
F6H8	1,3432
F6H9	1,3494

[0038] A low contact angle of less than 90° indicates high wettability and/or spreading, whereas a higher contact angle indicates poor wettability and spreading. Perfect wetting and spreading results in a contact angle of 0°, also reported as no measurable contact angle.

[0039] The inventors have found that the SFA's used in the present invention, in particular the preferred SFA's, exhibit an excellent wetting of various surfaces which are not easily wetted by conventional drug formulations. For example, the contact angle of both F4H5 and F6H8 on tablets compressed from either trospium chloride or fenofibrate (150 mg of drug substance compressed at 15-20 kN to tablets of 13 mm in diameter) was not measurable, i.e. perfect wetting occurred. It is noted that fenofibrate is an example of a hydrophobic, poorly water-soluble compound, whereas trospium chloride is hydrophilic and water-soluble. In comparison, the contact angle of purified water on the fenofibrate tablet was determined as 92.5°, i.e. the tablet was poorly wetted by water.

[0040] Moreover, the invention provides a means of formulating non-aqueous ophthalmic compositions which are microbiologically stable. This is due to the fact that SFA's are not normally prone to microbial contamination. Hence, it is possible to formulate preservative-free ophthalmic compositions which are better tolerable for many patients, in particular patients suffering from an ophthalmic disease.

[0041] In a further preferred embodiment, the non-aqueous vehicle having a density of at least 1.2 g/cm³ is selected to have a boiling point of at least about 120 °C. In the context of the present invention, it is advantageous in particular in the case of topical administration that the vehicle does not evaporate rapidly, but remains available for migrating towards the site of drug action and/or forming a drug depot at a site associated with the posterior segment of the eye. In another embodiment, the boiling point is at least about 125 °C.

[0042] According to a particular embodiment, the vehicle is also selected to exhibit a dynamic viscosity of not more than about 5 mPas, or not more than about 3.5 mPas, respectively. Depending on the exact formulation and mode of administration, it may be advantageous to use a low viscosity vehicle in order to achieve a sufficiently high rate of flux of the formulation from the site of administration to the posterior segment of the eye.

[0043] The composition of the invention may further comprise one or more additional excipients (other than the non-aqueous vehicle or vehicles). Such excipients may be selected from commonly known pharmaceutical ingredients which are physiologically tolerable and suitable for ophthalmic and/or parenteral use, depending on the intended mode of administration, such as from suitable cosolvents, surfactants, stabilisers, antioxidants, preservatives, colouring agents, and the like.

[0044] If a cosolvent is required, it should preferably be incorporated in a small amount. Potentially suitable organic cosolvents may be selected from glyceride oils, liquid waxes, and liquid paraffin, or an organic solvent exhibiting a high degree of biocompatibility. Examples of potentially useful oily excipients which may be used in combination with one or more SFA's include triglyceride oils (i.e. soybean oil, olive oil, sesame oil, cotton seed oil, castor oil, sweet almond oil), mineral oil (i.e. petrolatum and liquid paraffin), medium chain triglycerides (MCT), oily fatty acids, isopropyl myristate, oily fatty alcohols, esters of sorbitol and fatty acids, oily sucrose esters, or any other oily substance which is physiologically tolerated by the eye. In one of the preferred embodiments, the concentration of the oily excipient is up to about 30 wt.-%, such as in the range from about 0.1 to 20 wt.-%.

[0045] Examples of potentially useful organic solvents include glycerol, propylene glycol, polyethylene glycol, and ethanol. However, the concentration of the cosolvent should preferably be low relative to that of the SFA or SFA mixture. If an organic solvent such as ethanol is used, it is recommendable to keep it below a level of approx 5 wt.-%. More preferably, the content of ethanol is from about 0.1 to about 2 wt.-%, and most preferably not more than about 1 wt.-%.

[0046] Surfactants which are considered potentially useful include tyloxapol, poloxamers such as Pluronic F68LF or Lutrol F68, Pluronic L-G2LF and Pluronic L62D, polysorbates such as polysorbate 20 and polysorbate 80, polyoxyethylene castor oil derivatives, sorbitan esters, polyoxyl stearates, and mixtures of two or more thereof.

[0047] Furthermore, the invention provides a pharmaceutical kit comprising the composition as described above and a container holding the composition.

[0048] As already mentioned, the method, the composition and/or the kit according to the present invention is used in the treatment of a disease or condition affecting a tissue associated with the posterior segment of an eye of a patient. Examples of such diseases are age-related macular degeneration, diabetic retinopathy, glaucoma, retinitis pigmentosa, and cytomegalovirus retinitis, to mention only a few.

[0049] Depending on the disease which is to be treated, one or more suitable active ingredients may be incorporated,

e.g. in dissolved or dispersed form. As used herein, the dispersed form refers to a composition comprising at least two phases, i.e. a continuous or coherent phase (which is liquid in the case of the composition of the invention) and at least one dispersed (or internal, or incoherent) phase, which may be liquid if the system is an emulsion, or solid in the case of a suspension.

5 [0050] Suitable active ingredients include, e. g.,

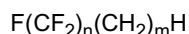
- prostaglandin analogues useful in the management of increased intraocular pressure, such as latanoprost, bimatoprost, tafluprost, travoprost and unoprostone;
- 10 - corticosteroids useful in the management of inflammatory processes, such as triamcinolone, dexamethasone, fluorometholone, hydrocortisone, prednisolone, and rimexolone;
- antibiotics, such as aureomycin, azithromycin, gentamycin, ciprofloxacin, ofloxacin, fusidic acid, kanamycin, levofloxacin, lomefloxacin, oxytetracyclin, tobramycin, natamycin, gentamycin, and moxifloxacin;
- 15 - beta-adrenergic antagonists useful for reducing the intraocular pressure, such as carteolol, timolol, metipranolol, betaxolol, pindolol, and levobunolol;
- cholinergic agents useful in the management of glaucoma, such as brimonidine, clonidine, dipivefrine, apraclonidine, carbachol, and pilocarpine;
- 20 - carbonic anhydrase inhibitors useful in the management of glaucoma, such as brinzolamide and dorzolamide;
- virustatic agents useful for ophthalmic administration, such as aciclovir, trifluridine, and ganciclovir; and
- 25 - nonsteroidal anti-inflammatory drugs, such as diclofenac, bromfenac, ketorolac, flurbiprofen, and indometacin,

including any salts and solvates thereof.

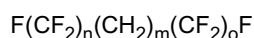
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Claims

1. A pharmaceutical composition for use in the treatment of a disease or condition of a tissue associated with the posterior segment of an eye of a patient, wherein the composition comprises an active pharmaceutical ingredient and a non-aqueous, physiologically tolerable, liquid vehicle having a density of at least 1.2 g/ml, wherein the liquid vehicle is a semifluorinated alkane according to the formula



40 or of formula

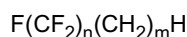


- 45 wherein n, m and o are independently selected in the range from 3 to 20;
 wherein the treatment comprises periocular injection and wherein the treatment further includes a time period subsequent to the administration of the composition during which period the patient is in a supine position facing upwards, said period being sufficient to allow the composition to migrate from the site of administration to a site in the posterior segment of the eye.

- 50 2. The pharmaceutical composition of claim 1, wherein the patient is affected by a disease or condition selected from age-related macular degeneration, diabetic retinopathy, glaucoma, retinitis pigmentosa, and cytomegalovirus retinitis.

- 55 3. The pharmaceutical composition of any preceding claim, wherein the composition further comprises a liquid vehicle selected from perfluorocarbons and/or polysiloxanes.

4. The composition of any preceding claim, wherein the semifluorinated alkane is a compound of formula

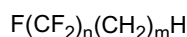


wherein n, m and o are independently selected from 3 to 10.

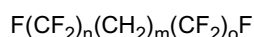
- 5 5. The composition of claim 4, wherein the semifluorinated alkane is selected from $F(CF_2)_4(CH_2)_5H$, $F(CF_2)_6(CH_2)_6H$ and $F(CF_2)_6(CH_2)_8H$.
6. The pharmaceutical composition of any preceding claim, wherein the liquid vehicle has a density of at least 1.35 g/ml.
- 10 7. The pharmaceutical composition of any preceding claim, wherein the liquid vehicle has a boiling point of at least 120 °C.
8. The pharmaceutical composition of any preceding claim, wherein the liquid vehicle has a refractive index in the range from 1.29 to 1.35 at 20°C.
- 15 9. The pharmaceutical composition of any preceding claim, comprising an active pharmaceutical ingredient in dissolved or dispersed form, which active ingredient is optionally selected from latanoprost, bimatoprost, tafluprost, travoprost, unoprostone, triamcinolone, dexamethasone, fluorometholone, hydrocortisone, prednisolone, rimexolone, aureomycin, azithromycin, gentamycin, ciprofloxacin, ofloxacin, fusidic acid, kanamycin, levofloxacin, lomefloxacin, oxytetracyclin, tobramycin, natamycin, gentamycin, moxifloxacin, carteolol, timolol, metipranolol, betaxolol, pindolol, levobunolol, brimonidine, clonidine, dipivefrine, apraclonidine, carbachol, pilocarpine, brinzolamide, dorzolamide, aciclovir, trifluridine, ganciclovir, diclofenac, bromfenac, ketorolac, flurbiprofen, and indometacin, including any salts and solvates thereof.
- 20 10. The pharmaceutical composition of any preceding claim, further comprising one or more excipients selected from co-solvents, surfactants, stabilisers, antioxidants, preservatives, and colouring agents.
- 25 11. The pharmaceutical composition of any preceding claim, wherein the treatment comprises periocular injection and wherein the pharmaceutical composition forms a depot in the retrobulbar region from which an active ingredient incorporated is released gradually over time.
- 30 12. The pharmaceutical composition of claim 1, wherein said time period is at least 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, or 6 hours, respectively.

35 **Patentansprüche**

- 40 1. Pharmazeutische Zusammensetzung zur Verwendung bei der Behandlung einer Krankheit oder eines Zustands eines Gewebes, das mit dem hinteren Segment eines Auges eines Patienten assoziiert ist, wobei die Zusammensetzung einen pharmazeutischen Wirkstoff und ein nicht-wässriges, physiologisch verträgliches flüssiges Vehikel mit einer Dichte von mindestens 1,2 g/ml umfasst, wobei das flüssige Vehikel ein semifluoriertes Alkan gemäß der Formel



45 oder der Formel



50 ist,

wobei n, m und o unabhängig voneinander aus dem Bereich von 3 bis 20 ausgewählt sind;
wobei die Behandlung periokulare Injektion umfasst, und wobei die Behandlung zudem eine Zeitspanne nach der Verabreichung der Zusammensetzung umfasst, wobei sich der Patient während der Zeitspanne in einer Rückenlage befindet und nach oben schaut, wobei die Zeitspanne hinreicht, dass die Zusammensetzung von der Verabreichungsstelle zu einer Stelle im hinteren Segment des Auges wandern kann.

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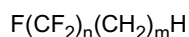
2. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei der Patient von einer Krankheit oder einem Zustand

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betroffen ist, die/der aus altersbedingter Makuladegeneration, diabetischer Retinopathie, Glaukom, Retinitis pigmentosa und Cytomegalievirus-Retinitis ausgewählt ist.

5 3. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, wobei die Zusammensetzung zudem ein flüssiges Vehikel umfasst, das aus Perfluorkohlenwasserstoffen und/oder Polysiloxanen ausgewählt ist.

4. Zusammensetzung nach einem vorhergehenden Anspruch, wobei das semifluorierte Alkan eine Verbindung der Formel



ist,

wobei n, m und o unabhängig voneinander aus 3 bis 10 ausgewählt sind.

15 5. Zusammensetzung nach Anspruch 4, wobei das semifluorierte Alkan aus $F(CF_2)_4(CH_2)_5H$, $F(CF_2)_6(CH_2)_6H$ und $F(CF_2)_6(CH_2)_8H$ ausgewählt ist.

6. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, wobei das flüssige Vehikel eine Dichte von mindestens 1,35 g/ml hat.

7. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, wobei das flüssige Vehikel einen Siedepunkt von mindestens 120°C hat.

8. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, wobei das flüssige Vehikel bei 20°C einen Brechungsindex im Bereich von 1,29 bis 1,35 hat.

9. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, umfassend einen pharmazeutischen Wirkstoff in gelöster oder dispergierter Form, wobei der Wirkstoff gegebenenfalls ausgewählt ist aus Latanoprost, Bimatoprost, Tafluprost, Travoprost, Unoproston, Triamcinolon, Dexamethason, Fluormetholon, Hydrocortison, Prednisolon, Rimexolon, Aureomycin, Azithromycin, Gentamycin, Ciprofloxacin, Ofloxacin, Fusidinsäure, Kanamycin, Levofloxacin, Lomefloxacin, Oxytetracyclin, Tobramycin, Natamycin, Gentamycin, Moxifloxacin, Carteolol, Timolol, Metipranolol, Betaxolol, Pindolol, Levobunolol, Brimonidin, Clonidin, Dipivefrin, Apraclonidin, Carbachol, Pilocarpin, Brinzolamid, Dorzolamid, Aciclovir, Trifluridin, Ganciclovir, Diclofenac, Bromfenac, Ketorolac, Flurbiprofen und Indometacin, einschließlich deren Salze und Solvate.

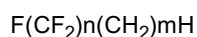
10. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, zudem umfassend einen oder mehrere Exzipienten, ausgewählt aus Colösungsmitteln, oberflächenaktiven Mitteln, Stabilisatoren, Antioxidationsmitteln, Konservierungsmitteln und Farbstoffen.

11. Pharmazeutische Zusammensetzung nach einem vorhergehenden Anspruch, wobei die Behandlung periokulare Injektion umfasst, und wobei die pharmazeutische Zusammensetzung in der retrobulbären Region ein Depot bildet, aus dem ein enthaltener Wirkstoff mit der Zeit allmählich freigesetzt wird.

12. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei die Zeitspanne mindestens 15 Minuten, 30 Minuten, 1 Stunde, 2 Stunden, 3 Stunden, 4 Stunden bzw. 6 Stunden beträgt.

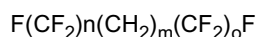
Revendications

1. Composition pharmaceutique destinée à être utilisée dans le traitement d'une maladie ou d'un état d'un tissu associé au segment postérieur d'un oeil d'un patient, la composition comprenant un principe actif pharmaceutique et un véhicule liquide non aqueux, physiologiquement tolérable, ayant une densité d'au moins 1,2 g/ml, le véhicule liquide étant un alcane semi-fluoré selon la formule



ou de la formule

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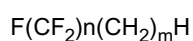


dans lesquelles n, m et o sont choisies indépendamment dans l'intervalle de 3 à 20 ;
le traitement comprenant une injection périoculaire et le traitement comprenant en outre une période, postérieure
à l'administration de la composition, durant laquelle le patient est dans une position couchée sur le dos, ladite
période étant suffisante pour permettre à la composition de migrer du site d'administration à un site situé dans
le segment postérieur de l'oeil.

2. Composition pharmaceutique selon la revendication 1, le patient est affecté d'une maladie ou d'un état choisi parmi
la dégénérescence maculaire liée à l'âge, la rétinopathie diabétique, le glaucome, la rétinite pigmentaire et la rétinite
à cytomégalovirus.

3. Composition pharmaceutique selon l'une quelconque des revendications précédentes, la composition comprenant
en outre un véhicule liquide choisi parmi les perfluorocarbones et/ou les polysiloxanes.

4. Composition selon l'une quelconque des revendications précédentes, l'alcane semi-fluoré étant un composé de la
formule



dans laquelle n, m et o sont choisis indépendamment dans l'intervalle de 3 à 10.

5. Composition selon la revendication 4, l'alcane semi-fluoré étant choisi parmi $F(CF_2)_4(CH_2)_5H$, $F(CF_2)_6(CH_2)_6H$ et
 $F(CF_2)_6(CH_2)_8H$.

6. Composition pharmaceutique selon l'une quelconque des revendications précédentes, le véhicule liquide ayant une
densité d'au moins 1,35 g/ml.

7. Composition pharmaceutique selon l'une quelconque des revendications précédentes, le véhicule liquide ayant un
point d'ébullition d'au moins 120 °C.

8. Composition pharmaceutique selon l'une quelconque des revendications précédentes, le véhicule liquide ayant un
indice de réfraction dans la gamme de 1,29 à 1,35 à 20 °C.

9. Composition pharmaceutique selon l'une quelconque des revendications précédentes, comprenant un principe actif
pharmaceutique sous forme dissoute ou dispersée, lequel principe actif est éventuellement choisi parmi le latano-
prost, le bimatoprost, le tafluprost, le travoprost, l'unoprostone, la triamcinolone, la dexaméthasone, la fluoromé-
tholone, l'hydrocortisone, la prednisolone, la rimexolone, l'aureomicine, l'azithromycine, la gentamycine, la cipro-
floxacin, l'ofloxacin, l'acide fusidique, la kanamycine, la lévofloxacin, la lomefloxacin, l'oxytétracycline, la to-
bramycine, la natamycine, la gentamycine, la moxifloxacin, le carteolol, le timolol, le métipranolol, le bétaxolo, le
pindolol, le lévobunolol, la brimonidine, la clonidine, la dipivérine, l'apraclonidine, le carbachol, la pilocarpine, le
brinzolamide, le dorzolamide, l'aciclovir, la trifluridine, le ganciclovir, le diclofénac, le bromfénac, le kétorolac, le
flurbiprofène et l'indométacine, y compris leurs sels et leurs solvates.

10. Composition pharmaceutique selon l'une quelconque des revendications précédentes, comprenant en outre un ou
plusieurs excipients choisis parmi les cosolvants, les tensioactifs, les stabilisants, les antioxydants, les conservateurs
et les agents colorants.

11. Composition pharmaceutique selon l'une quelconque des revendications précédentes, le traitement comprenant
une injection périoculaire et la composition pharmaceutique formant un dépôt dans la région rétrobulbaire à partir
de laquelle un principe actif incorporé est libéré progressivement dans le temps.

12. Composition pharmaceutique selon la revendication 1, ladite période étant d'au moins 15 minutes, 30 minutes, 1
heure, 2 heures, 3 heures, 4 heures ou 6 heures, respectivement.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2010062394 A [0012]
- WO 2008060359 A [0012]
- EP 965334 A [0028]
- EP 965329 A [0028]
- EP 2110126 A [0028]

Non-patent literature cited in the description

- **H. MEINERT et al.** *European Journal of Ophthalmology*, 2000, vol. 10 (3), 189-197 [0032]
- **H. MEINERT et al.** *Biomaterials, Artificial Cells, and Immobilization Biotechnology*, 1993, vol. 21 (5), 583-95 [0032]